Long-lasting tumor response on short-time administration of vemurafenib—A case report

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Key words: melanoma; short-time treatment; vemurafenib.

INTRODUCTION

Vemurafenib has been approved since 2011 in the United States for the treatment of advanced BRAF V600–mutated melanoma as first-line therapy. Although it significantly prolongs overall and progression-free survival, most patients relapse within 6 to 8 months owing to acquisition of drug resistance. New findings suggest that discontinuous dose administration of vemurafenib might prolong response to vemurafenib, but it is unclear whether modified cell signalling or other mechanisms, such as immune-mediated effects, are responsible for this effect.

CASE REPORT

We report on a 72-year-old patient with a 1.5-mm malignant melanoma on the right side of the chest, a positive axillary sentinel lymph node, and 0/11 positive lymph nodes at complete lymph node dissection diagnosed in August 2010. Adjuvant interferon therapy was declined by the patient. In December 2011, a cutaneous metastasis on the right side of the chest was excised.

In April 2012, other cutaneous, pulmonary and lymph node metastases occurred. Because of a positive BRAF V600E mutation status, vemurafenib (960 mg twice a day) was started. Eight days later, therapy was terminated by the patient because of side effects (angina pectoris, exanthema, and bloody stool). Because the patient declined further therapy, no subsequent treatment was performed. Surprisingly, follow-up computed tomography scans showed continuous partial regression of all metastases during the subsequent months (Figs 1, *A* and *B* and 2, *A* and *B*). Likewise, initially increased levels of S100β, lactate dehydrogenase, and C-reactive protein returned to normal 1 month after vemurafenib treatment and remained within normal levels. There is no evidence of tumor progression 24 months after short-time treatment with vemurafenib.

DISCUSSION

In this case, a short-term administration of vemurafenib might have caused profound and long-lasting antitumor effects. Because tumor lesions continued to regress during the months after therapy cessation, direct antitumor effects of vemurafenib are unlikely to account for this effect. Instead, we suggest that immune responses may play a crucial role, either because of the release of tumor antigens from vemurafenib-induced melanoma cell death or direct immunomodulatory effects of vemurafenib. Indeed, vemurafenib was found to stimulate immune recognition by increasing major histocompatibility complex expression by tumor cells,[1] elevating serum levels of interferon gamma, chemokine ligand 4, and tumor necrosis factor-α[2] and restoring compromised dendritic cell function,[3] resulting in elevated numbers of tumor-infiltrating lymphocytes in patients[4] and enhanced antitumor activity of adoptive immunotherapy in mice.[5] Thus, short-term or intermittent vemurafenib treatment may be considered as an adjunct for melanoma immunotherapy (eg, with cytotoxic T-lymphocyte antigen 4 or phosphodiesterase-1 antibodies).

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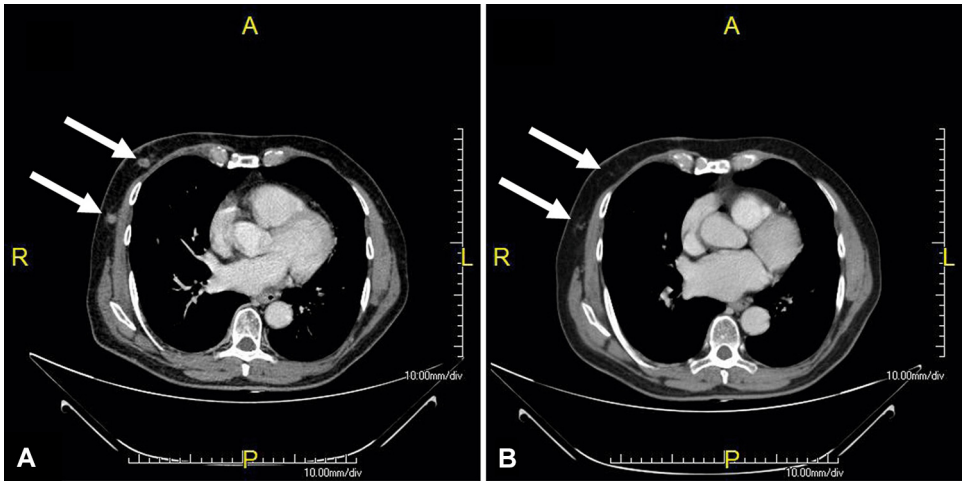

Fig 1. Cutaneous metastases before (**A**) and 13 months after (**B**) short-term vemurafenib treatment.

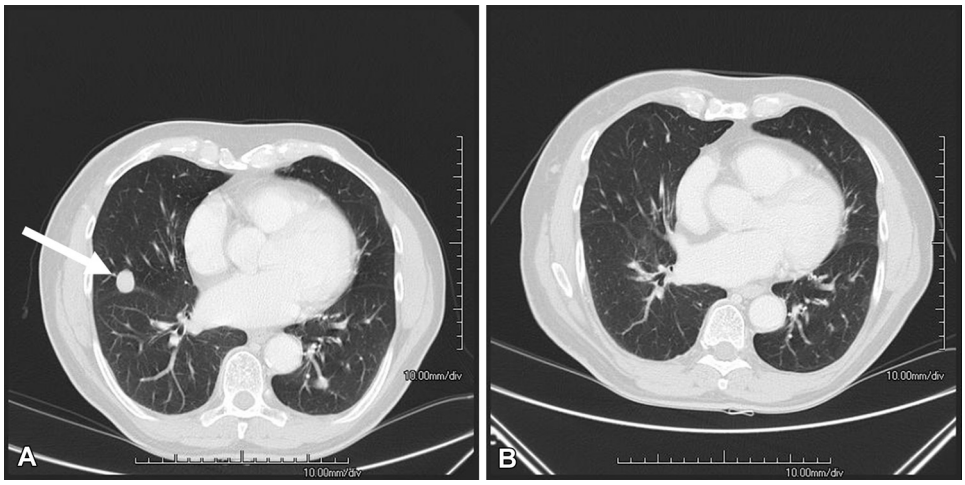

Fig 2. Pulmonary metastasis before (**A**) and 19 months after (**B**) short-term vemurafenib treatment.

REFERENCES

1. Sapkota B, Hill CE, Pollack BP. Vemurafenib enhances MHC induction in BRAF V600E homozygous melanoma cells. *Oncoimmunology*. 2013;2:e22890.
2. Wilmott JS, Haydu LE, Menzies AM, et al. Dynamics of Chemokine, Cytokine, and Growth Factor Serum Levels in BRAF-Mutant Melanoma Patients during BRAF Inhibitor Treatment. *J Immunol*. 2014;192:2505-2513.
3. Ott PA, Henry T, Baranda SJ, et al. Inhibition of both BRAF and MEK in BRAF(V600E) mutant melanoma restores compromised dendritic cell (DC) function while having differential direct effects on DC properties. *Cancer Immunol Immunother*. 2013; 62:811-822.
4. Frederick DT, Piris A, Cogdill AP, et al. BRAF inhibition is associated with enhanced melanoma antigen expression and a more favorable tumor microenvironment in patients with metastatic melanoma. *Clin Cancer Res*. 2013;19: 1225-1231.
5. Liu C, Peng W, Xu C, et al. BRAF inhibition increases tumor infiltration by T cells and enhances the antitumor activity of adoptive immunotherapy in mice. *Clin Cancer Res*. 2013;19: 393-403.